II. REMARKS

Claims 1 to 20 are pending in the subject application. By this Amendment and Response, claims 4, 5, 7, 9, 10, 18 and 19 have been amended. New claim 20 has been added. Support for the amendments to the claims and the addition of the new claim is found in the specification on page 3, lines 7 to 9; page 6, lines 17 to 23; page 7, and line 19 to page 8 line 11. Accordingly, an issue of new matter is not raised by these amendments and entry thereof is respectfully requested.

The amendments to the claims and the addition of the new claims is not intended to be a dedication to the public of the claims as originally presented. Applicants respectfully reserve the right to file the same or similar claims in a related application.

In view of the preceding amendments and the following remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested.

35 U.S.C. § 103

Claims 1-3, 18-19 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Upadhya et al (Hepatology 1997; 26:922-928) in view of Kottirsch et al (US Patent 6,500,983). The Office alleged that Upadhya teaches the potential use of MMP inhibitors in preserving the liver's sinusoidal endothelial lining (citing pages 927-928, last 3 paragraphs) and that such methodologies are effective in animal models for liver transplant studies (citing pages 922-924). The Office acknowledged that Upadhya does not expressly administer MMP inhibitors to humans susceptible of developing Sinusoidal Obstructive Syndrome. The Office also alleged that Kottirsch teaches the use of MMP inhibitors for treating conditions that are medicated [sic] by the over-production of MMP (citing column 12, line 65- column 13, line 39; column 15, lines 45-50). The Office concluded that it therefore would have been obvious to one of ordinary skill in the art at the time the invention was made to administer an MMP inhibitor, such as those described by Kottirsch, to patients susceptible to increased activity of MMP, such as patients post liver transplant, because, as taught by Upadhya, there would have been a reasonable expectation of success that administration of such agents would preserve sinusoidal endothelial cell lining in such patients.

Applicant respectfully traverses the grounds for rejection under 35 U.S.C. § 103.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Office must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally

available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *See Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001) ("In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention."); *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998) (a showing of a suggestion, teaching, or motivation to combine the prior art references is an "essential evidentiary component of an obviousness holding"); *Northern Telecom v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990) ("It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor."). The teachings or suggestions, as well as the second requirement, expectation of success, must come from the prior art, not applicant's disclosure. *See In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *See In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). *See also, In re Zurko*, 258 F.3d 1379, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001) (deficiencies of references cannot be saved by appeals to "common sense" and "basic knowledge" without any evidentiary support.).

In traverse, Applicant submits that the Office has failed to establish a *prima facie* case of obviousness for the following reasons. It would not have been obvious to one of ordinary skill in the art at the time the application was filed or at the time the invention was made that patients are susceptible to increased activity of MMP subsequent to radiation or chemotherapy. Moreover, even if such patients had been known to have increased MMP activity, it was not obvious to one of ordinary skill in the art that treatment with MMP-inhibitors would prevent the disease.

As a preliminary matter, the disease studied by Upadhya, cold preservation injury, is not the same disease as those that are the subject of the present invention, namely Sinusoidal Obstruction Syndrome and chemotherapy- or radiation-induced liver disease. Neither Upadhya nor Kottirsch teach that the same mechanism causes Sinusoidal Obstruction Syndrome and chemotherapy- or radiation-induced liver disease as that which causes cold preservation injury. Moreover, Upadhya never indicated that Sinusoidal Obstruction Syndrome and chemotherapy- or radiation-induced liver disease are caused by an over-production of MMPs that could be prevented by treating with an MMP inhibitor.

In addition, while the Upadhya reference showed that there was an association between MMP production and liver disease, a causal relationship was never shown between the production of MMPs and the expression of disease. This deficiency in the teaching of the reference is not made obvious by the addition of the teachings of Kottirsch as it is not directed to Sinusoidal Obstruction Syndrome and chemotherapy- or radiation-induced liver disease and production of MMP. The Kottirsch reference also fails to teach or suggest that these diseases are caused by over-expression of MMP. Hence, there is no motivation within Kottirsch to use MMP inhibitors as a prophylaxis or for treating Sinusoidal Obstruction Syndrome, or chemotherapy- or radiation-induced liver disease in human patients. Conversely, Applicant showed that MMP levels are increased in an experimental model of sinusoidal obstruction syndrome and that treatment with MMP inhibitors prevented and treated the disease. Thus, the requisite motivation to combine the references is absent from the Office's *prima facie* case.

Hence, none of the cited references, alone or in combination, teach or suggest the invention of the amended claims, i.e., administration of an MMP inhibitor to a specified patient population. Accordingly, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. § 103 is respectfully requested.

Claim Objections

Claims 18 and 19 stand objected to under 37 CFR 1.75(c), for allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant has amended these claims and respectfully traverses. Applicant maintains that claims 18 and 19 each further limit the base claim from which each depends. For example, claim 1 is directed to "a method for prophylaxis or treating Sinusoidal Obstruction Syndrome . . . in a patient in need thereof" and dependent claim 18 further limits this base claim to those patients

who are symptomatic for or suffer from Sinusoidal Obstruction Syndrome. The base claim is broader as it also includes patients who are not symptomatic yet who could benefit from prophylaxis or treatment, e.g., those patients who have just undergone radiation or chemotherapy and have increased MMP levels. Likewise, claim 19 further limits claims 2, 11 and 16 to those patients who suffer from chemotherapy- or radiation-induced liver disease. These claims further limit the base claims which are also directed to patients who are in need of therapy or prophylaxis and who may not yet be symptomatic for SOS.

Claims 4-17 are objected to as being dependent upon a rejected base claim. Examiner noted that they would allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claim.

Applicant has amended claims 4, 5, 7, and 9-10 and added claim 20 to include all the limitations of the base claim and any intervening claims. Because claims 11 and 16 were already in independent form, no amendments were made to those claims or to their corresponding dependent claims 12-15 and 17.

III. CONCLUSION

If the Examiner determines that a telephonic interview would advance prosecution of the application, the Examiner is invited to telephone Jennifer Phelps at (213) 680-6459.

If the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-2518**, referencing no. 7000692001. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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